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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,721	02/09/2004	Ralf Jockers	FRAV2003/0005USNP	9535

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EXAMINER
WOLLENBERGER, LOUIS V

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,721	JOCKERS ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-11,18-41,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15 and 42* is/are rejected.

7)☒ Claim(s) *14, 16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' timely election without traverse of Group II, claims 12–17 and 42–44 in the reply filed on July 28, 2005, is acknowledged. Also acknowledged is applicants' further election of SEQ ID NO:37 for prosecution on the merits with Group II.

It is noted that in their reply applicants refer to the election of SEQ ID NO:37 as an election of "species." However, applicants are herein advised that the different oligonucleotide sequences claimed in the instant application are not considered to be different species, but rather unrelated, structurally and functionally independent and distinct inventions (see page 10 of the restriction requirement). Thus, for purposes of the following examination, applicants are advised that the election of SEQ ID NO:37 is not an election of species but an election of a single oligonucleotide invention.

Status of the application

Claims 1–11, 18–41, and 43–44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 28, 2005. Claims 43 and 44 are withdrawn from further consideration as being drawn to a nonelected oligonucleotide sequence, SEQ ID NO:42.

Information Disclosure Statement

The information disclosure statement filed August 30, 2004, fails to comply with 37 CFR 1.97(d) because it lacks a statement as specified in 37 CFR 1.97(e). It has been placed in the application file, but the information referred to therein has not been considered as it pertains to WO03/072787, which is in French; no translation has been provided.

Foreign and Domestic Priority

Acknowledgment is made of applicants' claim for foreign priority under 35 U.S.C. 119(a)-(d) and for domestic priority under 35 U.S.C. 119(e). The certified copy of the foreign document, France 0301543, has been filed in parent Application No. 10/774,721 filed on Feb. 9, 2004.

Acknowledgment is also made of applicants' claim to the benefit of provisional application 60/461,005.

Objections to the Specification–Related applications

Pursuant to 37 CFR 1.78(2)(i), the specification is objected to for failing to include a reference to each prior-filed application to which benefit is claimed (see above; Foreign and Domestic Priority). Correction is required.

Objections to the Specification–Sequence Compliance

The disclosure is objected to because of the following: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid

sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The drawings identified as Fig. 1, 2, and 11A show nucleic acid sequences but these sequences are not identified by a "SEQ ID NO:" as required. The sequences must be unambiguously identified either in the drawing itself or in the Brief Description of the Drawings in the specification. For example, applicants have provided descriptions of the drawings on pages 23-25 of the specification, but the identifiers are missing or, as in the description for Fig. 11a, not clearly matched with the sequences in the figures. In order to be fully responsive to this Office Action, Applicant should review this application in its entirety to ensure compliance with the requirements of 37 CFR 1.821 through 1.825 and to make all appropriate corrections.

Claim Objections

Claims 14, 16, and 17 are objected to because of the following informalities: The claims refer to withdrawn claims. Appropriate correction is required.

*****

Claims 16 and 17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, claims 16 and 17 have not been further treated on the merits.

It is noted that claim 15, which is also a multiple dependent claim, refers to "either of claims 13 and 14." Claim 15 will be treated on the merits; however, it is suggested that the phrase be amended to recite "either of claims 13 or 14" so that it is clear that claim 15 refers to claims 13 and 14 in the alternative only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 16 recite the limitation "a vector" or "a cell". There are insufficient antecedent bases for these limitations in the claims.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 12 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. (US Patent 5,945,336).

Claim 12 is drawn to "an oligonucleotide of the iRNA type comprising from 10 to 60 nucleotides, which hybridizes specifically to polynucleotide sequence SEQ ID NO:21 and which inhibits expression of OB-RGRP."

Broadest reasonable interpretation of Claim 12 includes single stranded and double stranded oligonucleotides, 10 to 60 nt in length, that hybridize specifically to SEQ ID NO:21 and that interfere with the expression of OB-RGRP, which is presumed to be enoded by SEQ ID NO:21.

The term "hybridize specifically" is not clearly defined in the instant application. Applicants describe (page 14) specific procedural steps, such as buffers and incubation temperatures, for ensuring for what is referred to as "high stringency hybridization conditions"; however, it is unclear how these conditions equate to the minimum percent identity required to obtain "specific hybridization" with SEQ ID NO:21. In view of this uncertainty, the following art is applied.

Brown et al. teach a 20-nucleotide antisense oligonucleotide, identified as SEQ ID NO: 14, designed to target interleukin-6 receptor mRNA. The Brown et al. oligo is 94.1% identical to SEQ ID NO:21 of the instant application (see result 17 of sequence results iss.res). Brown et al. teach that the oligonucleotide can be either DNA or RNA, but is preferably DNA (column 7, lines 19-21). Because the Brown et al. oligo meets all the structural limitations recited in Claim 12, and because it exhibits high sequence identity with a sequence of SEQ ID NO:21, the cited oligo may be expected to "specifically hybridize" with SEQ ID NO:21 under normal cell growth

conditions at 37 degrees Celsius. As a result, the Brown et al. oligo appears to be a potential inhibitor of OB-RGRP expression, as would any other RNA oligo that showed a high probability of "specifically hybridizing" with SEQ ID NO:21 in the cell.

Accordingly, Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. (US Patent 5,945,336).

MPEP §2112 Requirements of Rejection Based on Inherency; Burden of Proof
A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12–15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (US Patent Application 2003/0166847); Agrawal and Tang (WO 94/01550); Taylor et al. (1999) *Drug Discvery Today* 4:562–567; Bennet et al. (US Patent 5,998,148); and Baracchini et al. (US Patent 5,801,154).

Claims 12 and 13 are drawn to a single or double stranded interfering RNA, comprising from 10 to 60 nucleotides, which hybridizes specifically to polynucleotide sequence SEQ ID NO:21 and which inhibits expression of OB-RGRP. Dependent claims 14 and 15 are drawn to vectors and cells thereof.

Bailleul et al. (US Patent Application 2003/0166847) teaches a 874-bp cDNA sequence (SEQ ID NO:2; Figs. 1A-B) encoding human leptin receptor gene-related protein, or LRGRP, that is 99.4% identical to the first 874 base pairs of SEQ ID NO:21 of the instant application.

Bailleul et al. further teach the use of antisense DNA, RNA, or PNA molecules, antagonists, or inhibitors to LRGRP in pharmaceutical compositions for treatment of diseases associated with the expression of LRGRP (paragraphs 128–160 and 191–192, for example).

Bailleul et al. also teach the use of art-recognized methods for expressing antisense molecules from vectors and methods for introducing said vectors into cells (paragraphs 128-138). For example, at paragraph 136 it is taught that "…RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding LRGRP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly can be introduced into cell lines, cells or tissues."

US Patent Application 2003/0166847 goes on to teach (paragraph 192) that "An oligonucleotide based on the coding sequence of LRGRP, as shown in FIGS. 1A and 1B, is used to inhibit expression of naturally occurring LRGRP. The complementary oligonucleotide is designed from the most unique 5' sequence as shown in FIGS. 1A and 1B and used either to inhibit transcription by preventing promoter binding to the upstream nontranslated sequence or translation of an LRGRP-encoding transcript by preventing the ribosome from binding. Using an appropriate portion of the leader and 5' sequence of SEQ ID NO:2, an effective antisense oligonucleotide includes any 15-20 nucleotides spanning the region which translates into the signal or early coding sequence of the polypeptide as shown in FIGS. 1A and 1B." Thus, US

Patent Application 2003/0166847 teaches that the 5' end of the LRGRP, the end that is 99.4% identical to SEQ ID NO:21 of the instant application, should be used to design antisense molecules that will specifically hybridize with and inhibit LRGRP. Additionally, Bailleul et al. teach that a vector capable of expressing LRGRP, or a fragment or a derivative thereof, may also be administered to a subject to treat certain metabolic, reproductive, or developmental disorders, and that in those conditions where leptin receptor gene-related protein activity is not desirable, cells could be transfected with antisense sequences of LRGRP-encoding polynucleotides or provided with inhibitors of LRGRP (paragr. 98-99).

Bailleul et al. (US Patent Application 2003/0166847) does not teach the use of double stranded RNA as an inhibitor of LRGRP.

Agrawal and Tang teach self-stabilized, hairpin (i.e., double stranded) RNAs that form stable duplexes, resist nucleolytic degradation and activate Rnase H, without the disadvantages of oligonucleotides known in the art. (page 3 and 19, and see Figs. 1, 5, and 6). For example, at page 5, Agrawal and Tang teach that "The advantages of oligonucleotides according to the invention, known as self-stabilized oligonucleotides, arise from the presence of two structural features: a target hybridizing region and a self-complementary region. The target hybridizing region comprises an oligonucleotide sequence that is complementary to a nucleic acid sequence that is from a plant or animal virus, a pathogenic organism, or a cellular gene or gene transcript, the abnormal gene expression or product of which results in a disease state. The self-complementary region comprises an oligonucleotide sequence that is complementary to a nucleic acid sequence within the oligonucleotide. Thus, at least when the oligonucleotide is not hybridized to a target nucleic acid sequence, the oligonucleotide forms a totally or partially

double stranded structure that is resistant to nucleolytic degradation. [...] This results in oligonucleotides that activate RNase H, an important feature for the antisense therapeutic compound."

Agrawal and Tang further teach that the "... target hybridizing region is from about 8 to about 50 nucleotides in length" (page 9-10); that "In a preferred embodiment, there are about 10 intramolecular base-pairs formed in the self-stabilized oligonucleotide, with the 10 base pairs being consecutive and involving the 3'-most nucleotides. Of course, the intra-molecular base-pairing can be so extensive as to involve every nucleotide of the oligonucleotide. Preferably, this will involve a self-complementary region of about 50 nucleotides or less." (page 15); and that the "...target hybridizing region of oligonucleotides according to the invention may contain ribonucleotides, deoxyribonucleotides or any analogs of ribonucleotides or deoxyribonucleotides." (page 13). On page 10, it is stated that "For purposes of the invention, the term "oligonucleotide sequence that is complementary to a nucleic acid sequence" is intended to mean an oligonucleotide sequence (2 to about 50 nucleotides) that hybridizes to the nucleic acid sequence under physiological conditions,e.a., by Watson-Crick base paring (interaction between oligonucleotide and single-stranded nucleic acid) or by Hoogsteen base pairing. (interaction between oligonucleotide and doublestranded nucleic acid) or by any other means. Such hybridization under physiological conditions is measured as a practical matter by observing interference with the function of the nucleic acid."

It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use the cDNA sequence of Bailleul et al. (US Patent Application 2003/0166847) to generate antisense sequences, vectors, pharmaceutical compositions, and transfected cells as

taught by Bailleul et al. (US Patent Application 2003/0166847) for inhibition of LRGRP expression.

In addition, because the cDNA sequence (SEQ ID NO:2) taught by Bailleul et al. in US Patent Application 2003/0166847 is 99.4% identical to the first 894-bp at the 5' end of SEQ ID NO:21 of the instant application, antisense oligos targeting and specifically hybridizing to the Bailleul et al. sequence would be expected to also target and specifically hybridize to SEQ ID NO:21 of the instant application, possibly leading to inhibition of expression of SEQ ID NO:21.

One would have been motivated to create such antisense compounds because US Patent Application 2003/0166847 expressly teaches that LRGRP is expressed in several cancer cell lines and tumor tissues (paragr. 96). Therefore, antagonists of LRGRP may either indirectly or directly interfere with tumor cell growth. Such cancers may include, but are not limited to, adenocarcinoma, sarcoma, leukemia, lymphoma, and cancers of the brain, breast, and bladder. Furthermore, it is suggested that an antagonist such as an antisense oligomer of LRGRP may be administered to a subject to treat a connective tissue disorder. Such disorders include, but are not limited to, rheumatoid arthritis and Sjogren's syndrome (paragr. 97).

One would have been motivated to make and use double stranded antisense compounds as taught by Agrawal and Tang because they teach that self-stabilized, or hairpin RNAs have greater resistance to nuclease degradation. Due to their longer half life, Agrawal suggests that lower effective dosages will be needed for therapeutic efficacy (page 19). This provides the advantages of increased duplex stability and RNase H activation, which are not both provided by any nuclease resistant oligonucleotide known in the art.

Finally, one would have had a reasonable expectation of success of making functionally active antisense oligos that specifically hybridize to and inhibit the expression of SEQ ID NO: 21 of the instant application given the teachings of US Patent Application 2003/0166847, described above, and given that Taylor et al. teaches that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known, that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Additionally, success and motivation would be expected in view of the teachings of Baracchini *et al.* (US Patent 5,801,154), who teach that antisense oligonucleotides can be used for research purposes. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett *et al.* (US Patent 5,998,148) are considered to parallel those of Baracchini *et al.* Bennett *et al.* teaches general antisense targeting guidelines at columns 3-4. Bennett *et al.* also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 10-24 teach numerous "carriers" for antisense oligonucleotides. Thus, Bennett *et al.* is also considered

to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

Thus, Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus, in the absence of evidence to the contrary, the invention as a whole, as claimed in the instant claims, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

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Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baracchini and Bennet (US Patent 5,510,239) and Agrawal and Tang (WO 94/01550).

Claim 42 depends from Claim 12 and is drawn to a double stranded interfering RNA in which at least one of the two strands comprises a sequence that is at least 60% identical to SEQ ID NO: 37 or 38.

Agrawal and Tang (WO 94/01550) is relied on for the reasons given above.

Agrawal and Tang (WO 94/01550) does not expressly teach an RNA oligonucleotide that is at least 60% identical to SEQ ID NO:37 or 38.

US Patent 5,510,239 teaches an antisense oligonucleotide, SEQ ID NO: 24, that is 20 nucleotides long, complementary to human multidrug resistance protein (MRP), and 65.7% identical to SEQ ID NO:37 of the instant application. (see result 1 of the sequence search of us-10-774-721-37.rni, issued US patents). At column 3, US Patent 5,510,239 teaches that "In the

context of this invention, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid or deoxyribonucleic acid."

Because the antisense oligo (SEQ ID NO:24) of US Patent 5,510,239 meets the minimum percent identity required by Claim 42, and because US Patent 5,510,239 teaches that "It is understood that an oligonucleotide need not be 100% complementary to its target nucleic acid sequence to be specifically hybridizable," (column 2, lines 35-39), it may be expected that the antisense oligo would specifically hybridize to and thereby inhibit SEQ ID NO:21, of the instant application, as recited in Claim 12.

One would have been motivated to make and use SEQ ID NO:24 of US Patent 5,510,239 as double stranded RNA to interfere with MRP expression, because Agrawal and Tang teach that it is advantageous to make and use duplex, hairpin antisense oligos for reasons of increased nuclease resistance and longer half life, and because US Patent 5,510,239 teaches that interference with MRP expression is desired for improving the efficacy of conventional methods of cancer chemotherapy, particularly of lung cancer, most particularly of small-cell lung cancer (column 1, lines 57-63).

Finally, one would have a reasonable expectation of success in view of the detailed teachings provided by Agrawal and Tang and US Patent 5,510,239, which provide detailed examples for the preparation and use of self-stabilized, self-complementary, antisense oligos.

Thus in the absence of evidence to the contrary, the invention claimed in claim 42 as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

*****

The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Rosen et al. (US Patent Application 2002/0044941), which discloses a 2732-bp polynucleotide sequence, SEQ ID NO:178, comprising SEQ ID NO:21 of the instant application (see result 3 of sequence search of published applications, us-10-774-721.rnpb). The sequence is identified as human leptin receptor gene-related protein (see Table 1, page 14 of the publication). Antisense RNAs are taught as being effective antagonists of the disclosed polynucleotides (see starting at paragraph 740, for example).

Bailleul et al. (1997) *Nuc. Acids Res.* 25:2752–2758, which teaches the complete, 1114 base pair, sequence of human leptin receptor gene-related protein. The sequence is 100% identical SEQ ID NO:21 of the instant application (see result 1 of the sequence search of us-10-774-721-21.rge).

Conclusion

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

September 1, 2005

TC 1600

Notice to Comply	Application No. 10/774,721	Applicant(s) Jockers et al.	
	Examiner Louis V. Wollenberger	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Sequences in drawing figures 1, 2, and 11A lack SEQ ID NO: identifiers. Identifiers must appear in the drawings themselves or in the descriptions of the drawings in the specification.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
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